HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AGRIFLU (Influenza Virus Vaccine) safely and effectively. See full prescribing information.

AGRIFLU, Influenza Virus Vaccine

Suspension for intramuscular injection

2009-2010 Formula

Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

AGRIFLU is an inactivated influenza virus vaccine indicated for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine.

AGRIFLU is approved for use in persons 18 years of age and older. (1)

This indication is based on the immune response elicited by AGRIFLU; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with AGRIFLU.

----------DOSAGE AND ADMINISTRATION----------

A single 0.5mL dose for intramuscular injection. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

AGRIFLU, a sterile suspension for injection, is supplied in 0.5 mL single-dose pre-filled syringes with no preservative. (3,11)

----------CONTRAINDICATIONS----------

History of hypersensitivity to egg proteins, kanamycin and neomycin or other components of the vaccine, or life-threatening reaction to previous influenza vaccination. (4.1, 11)

----------WARNINGS AND PRECAUTIONS----------

If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give AGRIFLU should be based on careful consideration of the potential benefits and risks. (5.1)

Immunocompromised patients may have a diminished immune response to AGRIFLU. (5.2)

----------ADVERSE REACTIONS----------

The most common (≥ 10%) local (injection-site) adverse reactions was injection site pain. (6)

The most common (≥ 10%) systemic adverse reactions were headache, myalgia, and malaise. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Vaccines at 1 800-244-7668 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------

Do not mix with any other vaccine in the same syringe. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Safety and effectiveness of AGRIFLU has not been established in pregnant women, nursing mothers, and children. (8.1, 8.2)

Antibody responses were lower in the geriatric population than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Issued: November 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

AGRIFLU® is an inactivated vaccine indicated for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine.
AGRIFLU is approved for use in persons 18 years of age and older. *(see CLINICAL STUDIES, [14])*
This indication is based on the immune response elicited by AGRIFLU; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with AGRIFLU.

2. DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake the contents of each syringe to aid inspection. Inspect AGRIFLU visually for the presence of particulate matter or discoloration prior to administration, whenever suspension and container permit. If either of these conditions exists, do not use the contents. *(see DESCRIPTION [11])*
Do not use the vaccine if it has been frozen.

2.2 Recommended Dose and Schedule

AGRIFLU should be administered as a single 0.5 mL intramuscular injection, preferably in the region of the deltoid muscle of the upper arm.
The vaccine should not be injected in the gluteal region or areas where there may be a major nerve trunk.

3. DOSAGE FORMS AND STRENGTHS

AGRIFLU is a sterile clear aqueous suspension for intramuscular injection supplied in 0.5 mL single-dose pre-filled syringes with no preservative. *(see DESCRIPTION [11])*

4. CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer AGRIFLU to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), kanamycin and neomycin, or any other constituent of the vaccine *(see DESCRIPTION [11]*), or to anyone who has had a life-threatening reaction to previous influenza vaccination.

5. WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give AGRIFLU should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence

The immune response to AGRIFLU in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals.

5.3 Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.4 Limitations of Vaccine Effectiveness

Vaccination with AGRIFLU may not protect all recipients.

6. ADVERSE REACTIONS

6.1 Overall Adverse Reactions

The most common local (injection site) adverse reactions observed in clinical studies with AGRIFLU were pain, induration, swelling, and erythema. The most common systemic adverse reactions observed were headache, myalgia, and malaise. These reactions are typically mild. Serious allergic reactions, including anaphylactic shock, have been observed during postmarketing surveillance in individuals receiving AGRIFLU.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice.

Clinical safety data have been obtained from two randomized, controlled trials.[1,2] In these trials, 2104 subjects were randomized to receive either AGRIFLU (1669 subjects) or a US-licensed comparator influenza vaccine (435 subjects) *(see CLINICAL STUDIES [14])*. Demographic and other baseline characteristics of the safety population from these two studies were comparable between the two vaccine groups (*see CLINICAL STUDIES [14]*). The percentages of subjects in both studies who had a record of receiving a previous influenza vaccination were 6% in the AGRIFLU group and 11% in the comparator group.

In both studies, solicited local (injection site) and systemic reactions were collected from subjects who completed a symptom diary card for four days following vaccination. Safety data are presented in Table 1.

Table 1: Percentage of Subjects Reporting Solicited Adverse Reactions in Days 1-4 After Vaccination With AGRIFLU or Comparator Influenza Vaccine

	Percentage of Subjects with Adverse Reactions			
	Study 1[1] 2007 NCT00464672 (18-64 years)		**Study 2[2] 2007-2008 NCT00617851** (18-49 years)	
	AGRIFLU N=460	Comparator[a] N=233	AGRIFLU N=1209	Comparator[a] N=202
Local Adverse Reactions				
Injection site pain				
Any pain	*25*	*30*	*22*	*20*
Severe pain[b]	*<1*	*0*	*<1*	*<1*
Induration	2	1	1	1
Swelling	<1	1	1	<1
Erythema	<1	1	<1	<1
Ecchymosis	<1	0	0	<1
Systemic Adverse Reactions				
Headache	20	16	22	22
Myalgia	13	15	16	19
Malaise	10	11	10	12

Fatigue	9	9	8	7
Chills	3	7	6	8
Arthralgia	5	6	5	6
Sweating	4	4	4	4
Fever (≥38°C)	1	2	3	3

[a]Comparator is U.S.-licensed trivalent, inactivated influenza virus vaccine (Fluvirin). [b] Severe injection site pain= local reaction leading to the inability to perform normal daily activities.

Unsolicited adverse events were reported by subjects over a 3-week period after vaccination. Unsolicited adverse events that occurred in > 1% of subjects included influenza-like illness (4% of AGRIFLU subjects and 3% of active comparator subjects) and headache (2% of AGRIFLU and comparator subjects). A total of 17% of subjects in both the AGRIFLU and the comparator groups reported unsolicited adverse events: 15% and 16% of subjects in the AGRIFLU and in the comparator groups, respectively, had mild unsolicited adverse events, 2% and 1% of subjects had moderate adverse events, and <1 % of subjects in both groups had severe adverse events.

6.3 Postmarketing Experience

The following additional adverse events have been identified during postapproval use of AGRIFLU in Europe since 2003. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and lymphatic system disorders:
Transient thrombocytopenia

Eye disorders:
Conjunctivitis, eyelid edema, eye redness

Gastrointestinal disorders:
Diarrhea, nausea, vomiting, abdominal pain

General disorders and administration site conditions:
Local injection site reactions, including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration, local lymphadenopathy, and general disorders including, chills, fever, malaise, fatigue, asthenia, facial edema.

Immune system disorders:
Hypersensitivity reactions (including throat and/or mouth edema, anaphylaxis, and anaphylactic shock)

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia.

Nervous system disorders:
Headache, syncope shortly after vaccination, dizziness, neuralgia, paraesthesia, convulsion, myelitis (including encephalomyelitis and transverse myelitis), neuropathy (including neuritis and brachial plexus neuropathy), paralysis (including Bell's Palsy and other cranial nerve paralyses), Guillain-Barré Syndrome

Vascular disorders:
Vasculitis (in rare cases associated with transient renal involvement), hot flush

7. DRUG INTERACTIONS

7.1 Concomitant Use With Other Vaccines

There are no data to assess the concomitant administration of AGRIFLU with other vaccines. If AGRIFLU is to be given at the same time as other injectable vaccine(s), the vaccine(s) should be administered at different injection sites.
AGRIFLU should not be mixed with any other vaccine in the same syringe.

7.2 Concurrent Use With Immunosuppressive Therapies

Immunosuppressive therapies including corticosteroids may reduce the immune response to AGRIFLU.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.
Reproduction studies have been performed in female rabbits at a dose approximately 15 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired fertility or harm to the fetus due to AGRIFLU. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, AGRIFLU should be given to a pregnant woman only if clearly needed.
In two reproduction toxicity studies, the effect of AGRIFLU on embryo-fetal or post-natal development was evaluated in pregnant rabbits. Animals were administered AGRIFLU 3 times prior to gestation, during the period of organogenesis (gestation day 7) and later in pregnancy (gestation day 20), 0.5 mL/rabbit/occasion (approximately 15-fold excess relative to the projected human dose on a body weight basis) by intramuscular injection. Effects on post-natal development could not be fully evaluated, however, there were no adverse effects attributable to the vaccine on mating, female fertility, pregnancy, or embryo-fetal development. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

8.3 Nursing Mothers

AGRIFLU has not been evaluated in nursing mothers. It is not known whether AGRIFLU is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AGRIFLU is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

8.5 Geriatric Use

In eight clinical studies, 1221 subjects 65 years of age and older received AGRIFLU. Antibody responses in geriatric subjects were lower after administration of AGRIFLU in comparison to younger adult subjects. Adverse event rates were generally similar in frequency in geriatric subjects (≥65 years of age) to those reported in younger adults, although some differences were observed.

11. DESCRIPTION

AGRIFLU, Influenza Virus Vaccine, for intramuscular injection is a trivalent inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs inoculated with an influenza virus suspension containing kanamycin and neomycin sulphate. Each of the influenza virus strains is harvested and clarified separately by centrifugation and filtration prior to inactivation with formaldehyde. The inactivated virus is concentrated and purified by zonal centrifugation. The surface antigens, hemagglutinin and neuraminidase, are obtained from the influenza virus particle by further centrifugation in the

presence of cetyltrimethylammonium bromide (CTAB), a process which removes most of the internal proteins. The CTAB is removed from the vaccine preparation by subsequent purification steps.

AGRIFLU is a sterile clear aqueous suspension and is formulated to contain a total of 45 mcg hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following three influenza virus strains recommended for the 2009/2010 influenza season: A/Brisbane/59/2007, IVR-148 (H1N1); A/Uruguay/716/2007, NYMC X-175C (H3N2) (an A/Brisbane/10/2007-like virus); and B/Brisbane/60/2008.

AGRIFLU is manufactured and formulated without thimerosal or any other preservative. Each 0.5 mL dose may contain residual amounts of egg proteins (<0.4 mcg), formaldehyde (≤10 mcg), polysorbate 80 (≤50 mcg), and CTAB (≤12 mcg). Each dose may also contain residual amounts of neomycin (≤0.02 mcg by calculation) and kanamycin (≤0.03 mcg by calculation), which are used during the initial stages of manufacture. The syringe plunger does not contain latex.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of hemagglutination inhibition (HI) antibody titers induced by vaccination with inactivated influenza virus vaccine have not been correlated with protection from influenza illness. In some human studies, HI antibody titers of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects[3].

Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinin of influenza virus strains (typically two type A and one type B), representing the influenza viruses likely to be circulating in the United States in the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year[4].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

AGRIFLU has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility.

14. CLINICAL STUDIES

In two randomized, controlled clinical trials with AGRIFLU, immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of AGRIFLU. No controlled efficacy

trials have been performed to indicate a decrease in influenza disease after vaccination with AGRIFLU.

In the first clinical trial (Study 1[1]), performed in Argentina, 692 adult subjects were enrolled and randomized (460 and 232 for AGRIFLU and U.S. licensed comparator influenza vaccine, respectively). A total of 424 in the AGRIFLU group and 219 in the comparator group were evaluable subjects. Among the 424 recipients of AGRIFLU, 64% were women, and the distribution of subjects by ethnicity was 80% White, 19% Hispanic, and 1% Asian. In the AGRIFLU group the subjects' age ranged between 18 and 64 years, and the median age was 37 years. Among the 219 recipients of the U.S. licensed comparator influenza vaccine, 55% were women, and the distribution of subjects by ethnicity was 79% White and 21% Hispanic. In the comparator group the subjects' age ranged between 18 and 64 years, and the median age was 34 years.

In the second clinical trial (Study 2[2]), performed in the Dominican Republic, subjects were randomly assigned at a 2:2:2:1 ratio to receive either one of three consecutive AGRIFLU lots or the US-licensed influenza vaccine used for comparison of the safety profile. A total of 1507 adult subjects 18 to 49 years of age were enrolled (1290 and 217 for AGRIFLU and comparator influenza vaccine, respectively). Among the 1182 evaluable subjects vaccinated with AGRIFLU, 72% were women; 97.5% were Hispanic, 2% were Black, and 0.5% were of other ethnic origin. In the AGRIFLU group the subjects' age ranged between 18 and 49 years, and the median age was 30 years. Among the 194 recipients of the U.S. licensed comparator influenza vaccine, 73% were women; 98% were Hispanic, and 2% were Black. In the comparator group the subjects' age ranged between 18 and 49 years, and the median age was 31 years. For both studies, the following co-primary immunogenicity endpoints were assessed: 1) the lower bounds of the 2-sided 95% confidence intervals (CI) for the proportion of subjects with HI antibody titers of 1:40 or greater after vaccination, should exceed 70% for each vaccine antigen strain; and 2) the lower bounds of the 2-sided 95% CI for rates of seroconversion (defined as ≥ 4-fold increase in post-vaccination HI antibody titers from pre-vaccination titers of ≥ 1:10 or an increase in titers from < 1:10 to ≥ 1:40), should exceed 40% for each vaccine antigen strain. In both studies, the active comparator arm was used for comparison of safety only.

In both studies serum HI antibody responses 21 days after vaccination with AGRIFLU met the pre-specified co-primary endpoint criteria for all three viral strains included in the vaccine (Table 2). In addition, in Study 2, clinical consistency of three manufacturing lots of AGRIFLU was successfully demonstrated and pooled results are presented.

Table 2: Serum HI Antibody Responses in Adults 21 Days After Vaccination With AGRIFLU

	Vaccine Strain	% HI Titer ≥1:40 (95% CI)	% Seroconversion[b] (95% CI)
Study 1 2007 (18-64 years) NCT00464672 N=424	A/H1N1	93 (90-95)	74 (69-78)
	A/H3N2	96 (94-98)	72 (68-76)
	B	91 (87-93)	77 (72-81)

Study 2 2007-2008 (18-49 years) NCT00617851 N=1182 [a]	A/H1N1	98 (97-99)	94 (93-95)
	A/H3N2	99 (98-100)	67 (65-70)
	B	87 (85-89)	84 (82-86)

[a]pooled number of subjects receiving one of the three manufacturing lots of AGRIFLU. [b] Rates of seroconversion = percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer > 1:40 or a pre-vaccination HI titer > 1:10 and at least a four-fold rise in post-vaccination HI antibody titer.

15. REFERENCES

1 NCT00464672; see www.clintrials.gov

2 NCT00617851; see www.clintrials.gov

3 Hobson D, Curry RL, Beare A, et. al. The role of serum hemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972; 767-777.

4 Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Reports 2008; 57(RR-07):1-60. Centers for Disease Control and Prevention, Atlanta, GA.

16. HOW SUPPLIED/STORAGE AND HANDLING

AGRIFLU is supplied as a 0.5 mL single-dose pre-filled syringe in a package of 10 pre-filled syringes per carton without needles (NDC number: 46028-108-01). The syringe plunger does not contain latex.

Store at +2°C to +8°C (35°F to 46°F) (in a refrigerator), not frozen, and protect from light.

Allow the vaccine to reach room temperature and shake before use.

Do not use after the expiration date.

17. PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Provide the following information or instructions to vaccine recipients:

Inform on potential benefits and risks of immunization with AGRIFLU.

Explain that (1) AGRIFLU contains non-infectious particles and cannot cause influenza and (2) AGRIFLU is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against other respiratory illnesses.

Instruct to report any severe or unusual adverse reactions to their healthcare provider.

Instruct that annual vaccination is recommended.

AGRIFLU is a registered trademark of Novartis Vaccines and Diagnostics, Inc.

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